Environmental Health Perspectives Supplements
Vol. 101 (Suppl. 3): 21–26 (1993)

Mutagenicity Testing of 9-*N*-Substituted Adenines and Their *N*-Oxidation Products

by J. W. Gorrod,[1] C. Ioannides,[2] S. P. Lam,[1] and S. Neville[2]

Adenine together with certain 9-*N*-substituted derivatives such as 9-methyl, 9-benzyl, 9-benzhydryl, and 9-trityl were tested against *Salmonella typhimurium* strains TA97, TA98, and TA100 in the absence and presence of rat hepatic S9 prepared from Aroclor 1254 pretreated rats. All compounds were positive toward TA98 in the presence of the metabolic activating system, whereas they all lacked mutagenic activity in the absence of S9, and toward TA97 and TA100 with or without S9 when tested at 100 ng/plate. A similar pattern was observed for the corresponding 1-*N*-oxides. 6-Hydroxylaminopurine was not mutagenic toward TA100 at 100 ng/plate, whereas it was toxic toward TA97 and TA98 at this level. When tested at 1 ng/plate, hydroxylaminopurine was still toxic to TA98 but produced twice the spontaneous reversion rate to TA97 without metabolic activation. Surprisingly, 9-methyl-6-hydroxylaminopurine was only active toward TA98 in the presence of S9, whereas 9-benzyl-6-hydroxylaminopurine was highly active toward TA97 and TA100 in the absence of S9 and even more active in the presence of S9. This compound was inactive toward TA98 in the absence of S9. The results generally support the concept that nuclear *N*-oxidation of aminoazaheterocycles is a detoxication process, whereas *N*-hydroxylation of the exo amino group is a toxication reaction.

Introduction

Aminoazaheterocylcles are a class of compounds characterized by an aromatic nuclear nitrogen atom(s) together with an *ortho* exo-amino group. These compounds have diverse pharmacological properties, are widely used in clinical medicine, and occur as natural products [(*1–3*) Fig. 1] or are formed as metabolites of drugs (Fig. 2). They may also be produced during the cooking of foods or pyrolysis of proteins and amino acids [(*4,5*) Fig. 3].

The metabolism of many of these compounds has been studied (*1–3*), and generally it has been observed that compounds used in clinical medicine are not genotoxic and are metabolized by oxidation at one or more nuclear nitrogens (*6–12*), whereas those produced by pyrolysis are potent mutagens (*13*) and are metabolized by *N*-hydroxylation of the exo amino group (*14–16*). This has led to the concept (*1–3*) that nuclear *N*-oxidation of aminoazaheterocycles is a detoxication process, whereas *N*-hydroxylation of the exo amino group is a toxication reaction (Fig. 4).

Ortho aminoazaheterocycles are usually oxidized at either one or other of the constituent nitrogens. Only in the case of the nonmutagenic 2-aminopyridine has both pathways of *N*-oxidation been observed (*17,18*); di-*N*-oxygenation has never been found with these compounds. Direct proof of the toxication/detoxication concept of *ortho* aminoazaheterocycle metabolism and toxicity has therefore not been possible.

Adenine (Fig. 5) is a naturally occurring *ortho* aminoazaheterocycle that is capable of being chemically converted to both the 1-*N*-oxide (*19*) and 6-hydroxylaminopurine (*20*). Similar pairs of *N*-oxidation products may be prepared from 9-substituted adenines which themselves differ in their physicochemical properties (*12*). Certain 1-*N*-oxides and 6-hydroxylamine derivatives of 9-substituted purine have been compared with their parent compounds and used to probe the toxication/detoxication concept using various *Salmonella typhimurium* strains with and without a hepatic activation system.

Materials and Methods

Chemicals

Adenine, 9-methyladenine (MA), 9-benzyladenine (BA), and their corresponding 1-*N*-oxides (ANO, MANO, and BANO) and 6-hydroxylamines, i.e., 6-hydroxylamino-

[1]Chelsea Department of Pharmacy, King's College London, Manresa Road, London SW3 6LX, UK.
[2]Division of Toxicology, School of Biological Sciences, University of Surrey, Guildford, Surrey GU2 5XH, UK.
Address reprint requests to J. W. Gorrod, Chelsea Department of Pharmacy, King's College London, Manresa Road, London SW3 6LX, UK.

purine (HP) and 6-hydroxylamino-9-methylpurine (HMP) were obtained as described previously (*11*). 9-Benzhydryladenine (BHA), 9-benzhydryladenine-1-*N*-oxide (BHANO), 9-trityladenine (TA), and 9-trityladenine-1-*N*-oxide (TANO) were prepared according to previously reported methods (*12*).

6-Hydroxylamino-9-benzylpurine (HBP) was synthesized by the reaction of 9-benzyl-6-chloropurine with an ethanolic solution of hydroxylamine. Hydroxylamine hydrochloride (7.8 g) dissolved in boiling, absolute ethanol (130 mL) was mixed with a solution of potassium hydroxide (6.8 g) in hot ethanol (25 mL). The potassium chloride that formed was filtered off and washed three times with hot ethanol (15 mL). The ethanolic hydroxylamine solution obtained was added to a boiling solution of 9-benzyl-6-chloropurine (1.87 g), prepared according to the method of Montgomery and Temple (*21*), in absolute ethanol (78 mL). The mixture was refluxed for 6 hr, after which the solution was left to cool overnight. HBP precipitated; was collected, and recrystallized from absolute ethanol (yield 78%, melting point 226–228°C with decomposition). (Found: C,59.71: H,4.47; N,28.95%; $C_{12}H_{11}N_5O$ requires C, 59.74; H, 4.60; N, 29.03%.)

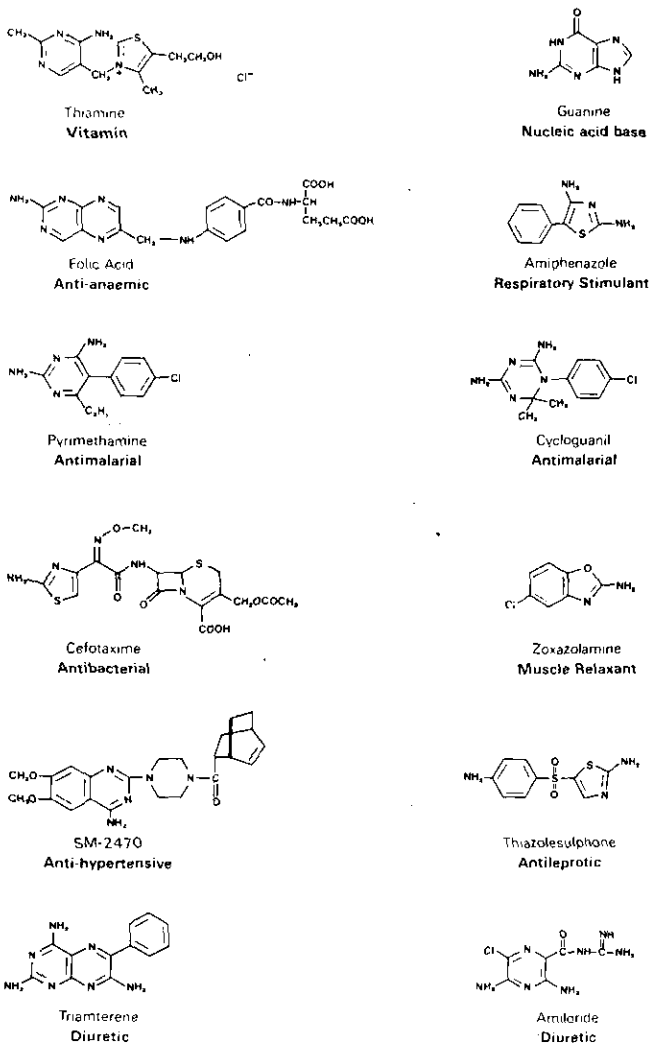

FIGURE 1. Examples of some medicinal and natural aminoazaheterocycles.

Determination of Mutagenic Potential

The compounds were tested against *Salmonella typhimurium* strains TA97, TA98, and TA100 exactly as described by Maron and Ames (*22*) at a concentration of 100 ng/plate or less dissolved in dimethylsulfoxide (1 μg/mL). The viability of the systems were checked by incorporating either 9-aminoacridine (20 μg/plate; TA97), 2-nitrofluorene (2 μg/plate; TA98), or methyl-*N*-nitro-*N*-nitrosoguanidine (2 μg/plate; TA100). 2-Aminoanthracene (5 μg/plate) was used with all strains in the presence of an S9 metabolic activating system. The S9 metabolic activating system was prepared from rats that had been pretreated with Aroclor 1254 (a single IP dose of 500 mg/kg, the animals were killed on day 5 after administration) and contained S9 at a 10% v/v suspension.

Results and Discussion

Adenine, together with its 1-*N*-oxide and 6-*N*-hydroxy derivative (Fig. 5) were tested for mutagenicity using *Salmonella typhimurium* TA97, TA98, and TA100 strains. Also tested were the 9-methyl and 9-benzyl derivatives and the 9-benzhydryl and 9-trityl derivatives of adenine and adenine-1-*N*-oxide. 9-Benzhydryl-6-hydroxylaminopurine and 9-trityl-6-hydroxylaminopurine were not tested due to the difficulty in obtaining the pure compounds (*23*). The results of the mutagenicity study carried out in the absence or presence of a metabolic activating system are presented in Table 1.

The results in the absence of a metabolic activating system may be summarized as follows: *a*) the parent purines did not demonstrate enhanced mutagenicity when compared with the spontaneous reversion rate; *b*) the purine-1-*N*-oxides had virtually identical mutagenic properties as the parent bases; *c*) the 6-*N*-hydroxylamines, where available, were generally more toxic and more mutagenic than the base or the *N*-oxide toward TA97 and TA100 but not toward TA98. This suggests that they may be acting by either an intercalating or base-pair mechanism. However, this was not true for the 9-methyl compound, which showed only a slight increase in mutagenic activity compared to either base or 1-*N*-oxide toward TA97 and lacked mutagenicity, at the level tested, toward TA100. A clear mutagenic response, over the base and 1-*N*-oxide, due to exo-amino *N*-hydroxylation was observed using the 9-benzyl series even though the latter compound was tested at only 50 ng/plate compared with 100 ng/plate for the parent purine and 1-*N*-oxide.

In the presence of a metabolic activating system, the results observed were *a*) the parent compounds were inactive toward TA97 and TA100, whereas they were active toward TA98; *b*) the 1-*N*-oxides were also inactive towards

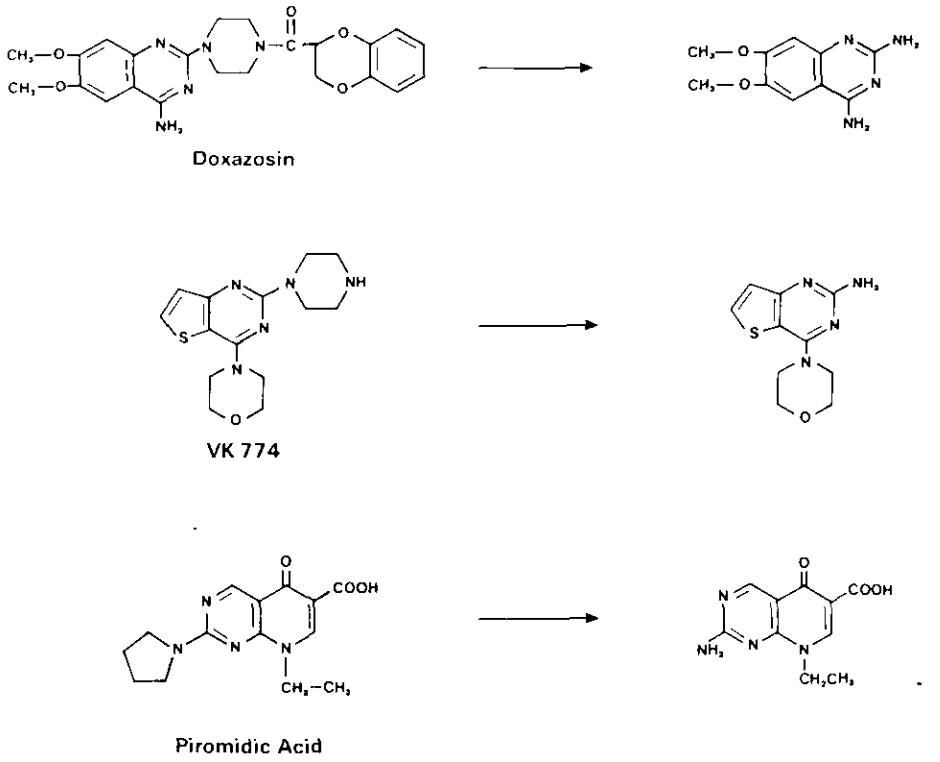

FIGURE 2. Examples of aminoazaheterocycles produced during metabolism of drugs.

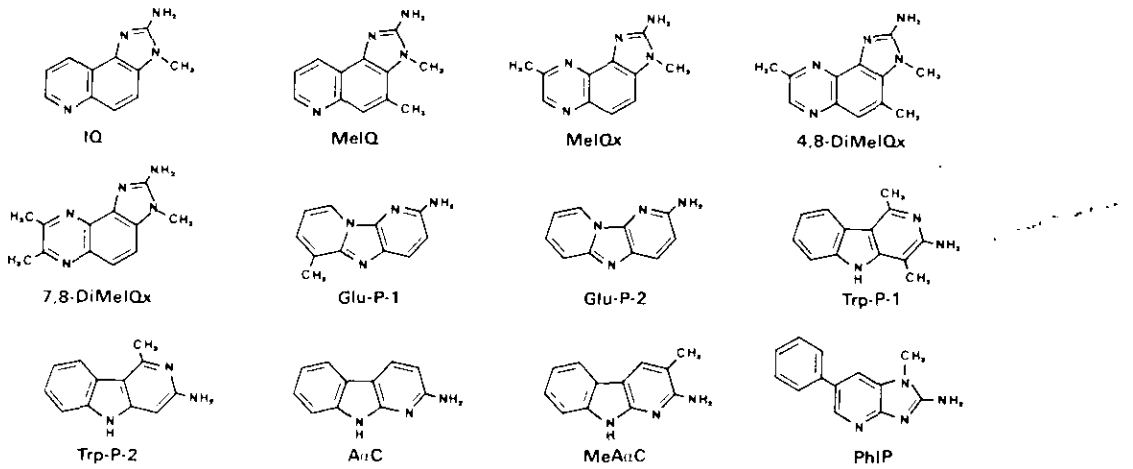

FIGURE 3. Examples of mutagenic aminoazaheterocycles formed during cooking of food or pyrolysis of proteins and certain amino acids.

TA97 and TA100 but again were active towards TA98; *c*) the hydroxylamines were active toward both TA97 and TA100 as well as TA98. Additionally, in all cases where mutagenic activity was demonstrated in the absence of a metabolic system, an enhanced mutagenic effect was observed after incorporation of the metabolic activating system. In the case of compounds that failed to demonstrate mutagenic activity (e.g., bases and 1-*N*-oxides in the absence of an activating system) addition of the system allowed mutagenic activity to be expressed.

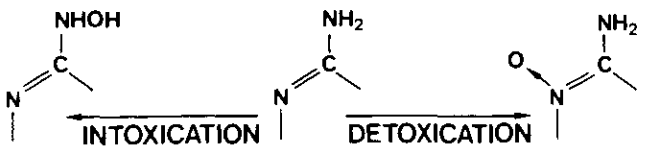

FIGURE 4. The metabolic intoxication/detoxication concept of aminoazaheterocycles.

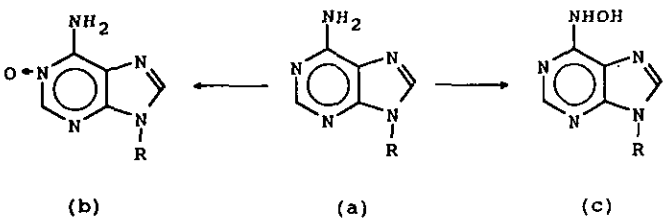

FIGURE 5. Structures of (*a*) 9-substituted adenine, (*b*) adenine-1-*N*-oxide, and (*c*) 6-hydroxylaminopurine. (I) R = H; (II) R = CH_3; (III) R = $CH_2C_6H_5$; (IV) R = $CH(C_6H_5)_2$; (V) R = $C(C_6H_5)_3$.

Previous studies on the metabolism of 9-substituted-adenines showed that they were only coverted to 1-*N*-oxides by a phenobarbital-inducible cytochrome P450 species, presumably CYP2B. This enzyme failed to oxidize adenine to adenine-1-*N*-oxide (*11,12,24*). Using rats pretreated with either 3-methylcholanthrene or isosafrole (inducers of CYP1), Clement and Kunze (*25*) demonstrated that adenine, at high substrate concentrations, was converted to 6-hydroxylaminopurine. It is likely that the activating system prepared from rats pretreated with Aroclor 1254 (an inducer of both CYP1 and CYP2B), used in the present study is also capable of metabolizing adenines to the corresponding 6-hydroxylaminopurines. However, as the 6-hydroxylaminopurines tested generally showed an enhanced activity in the presence of the activating system, it may be that further oxidation of the 6-hydroxylamino function is occurring, producing a nitroso or nitro compound or an intermediate nitrenium ion or nitroxide radical (*26,27*). Such intermediates are known to react with cellular macromolecules and may initiate their mutagenic effect via this mechanism (*28,29*).

The results obtained in the present work are generally consistent with previous observations on the genotoxicity of *N*-oxidized derivatives of aminopurines. Thus, 6-hydroxylaminopurine induced mitotic inhibition and nuclear degeneration in mouse sarcoma 180 cells *in vitro* and prolonged the survival time of mice bearing sarcoma 180 ascites cells (*30,31*). This substance is genotoxic to both eukaryotes and prokaryotes (*32–36*).

Our results agree with McCartney et al. (*35*), who also found that adenine was inactive toward TA100, whereas 6-hydroxylaminopurine was mutagenic. This latter compound was found by these authors to be inactive toward TA98, whereas in our experiments we found that HP was extremely toxic toward this strain.

It has been proposed that HP acts by forming a desoxynucleoside triphosphate, which is incorporated into DNA (*36*), although other evidence (*35*) indicates that the mutagenic activity of 6-hydroxylaminopurine is caused by direct adduct formation rather than by base incorporation. This is supported by results obtained using a series of *E.*

Table 1. Mutagenicity of adenine derivatives toward *S. typhimurium* strains with (+) and without (−) a metabolic activating system.[a]

	TA97		TA98		TA100	
Compound	−	+	−	+	−	+
Spontaneous reversion rate	65 ± 1	89 ± 1	16 ± 5	21 ± 4	99 ± 7	108 ± 13
I						
a. Adenine	63 ± 5	104 ± 12	21 ± 5	76 ± 11	108 ± 15	103 ± 26
b. Adenine-1-*N*-oxide	71 ± 11	95 ± 11	19 ± 6	124 ± 15	105 ± 10	117 ± 20
c. 6-Hydroxylaminopurine (1 ng/plate)	132 ± 55	113 ± 4	toxic	toxic	121 ± 13	170 ± 22
II						
a. 9-Methyladenine	73 ± 5	88 ± 4	21 ± 6	88 ± 20	111 ± 5	113 ± 7
b. 9-Methyladenine-1-*N*-oxide	61 ± 1	99 ± 10	24 ± 2	118 ± 9	105 ± 3	109 ± 3
c. 9-Methyl-6-hydroxylaminopurine	88 ± 4	103 ± 10	21 ± 1	96 ± 11	93 ± 15	123 ± 14
III						
a. 9-Benzyladenine	71 ± 11	92 ± 16	17 ± 1	131 ± 18	105 ± 9	123 ± 16
b. 9-Benzyladenine-1-*N*-oxide	76 ± 4	100 ± 14	20 ± 2	92 ± 11	102 ± 23	109 ± 3
c. 9-Benzyl-6-hydroxylaminopurine (50 ng/plate)	799 ± 18	1330 ± 216	17 ± 3	69 ± 8	944 ± 105	1664 ± 98
IV						
a. 9-Benzhydryladenine	69 ± 16	88 ± 4	18 ± 3	113 ± 13	89 ± 4	129 ± 13
b. 9-Benzhydryladenine-1-*N*-oxide	66 ± 7	91 ± 7	19 ± 4	107 ± 11	96 ± 12	131 ± 13
c. 9-Benzhydryl-6-hydroxylaminopurine	–	–	–	–	–	–
V						
a. 9-Trityladenine	73 ± 5	101 ± 14	18 ± 9	102 ± 7	86 ± 1	83 ± 18
b. 9-Trityladenine-1-*N*-oxide	61 ± 7	98 ± 9	23 ± 6	102 ± 41	81 ± 41	106 ± 13
c. 9-Trityl-6-hydroxylaminopurine	–	–	–	–	–	–
Positive control	1456	600	302	865	3464	3240

[a]Results are presented as histidine revertants/plate (mean ± SD of triplicates). Each study was repeated at least once. Unless otherwise stated, each compound was tested at a concentration of 100 ng/plate. Compounds were dissolved in dimethylsulfoxide (1 μg/mL). The activation system contained hepatic S9 fraction (10% v/v) from Aroclor 1254 pretreated rats.

coli mutants, which led Murray (*37*) to propose that "the major mechanism for hydroxylaminopurine is due to the reaction of these compounds with the O^6 position of guanine and the O^4 position of thymine."

Administration of 6-hydroxylaminopurine to 10 female Wistar rats produced only one tumor at 15 months and was completely inactive in Sprague-Dawley rats; the authors (*38*) concluded that "its oncogenicity is marginal at best." Barrett (*33*), citing the same publication (*38*), interprets the data as meaning that HP is weakly carcinogenic; this is supported by the present studies where HP only displayed a weak mutagenic response. 6-Hydroxylaminopurine is also teratogenic (*30*).

Studies on the toxicity of adenine-1-*N*-oxide are more controversial. In an early publication (*39*), it was stated that "Administration of adenine-1-*N*-oxide for 6 months failed to produce tumors in any tissues of 13 rats during the experimental period of 15 months." In a later paper (*38*), it was reported that "Subsequent assays have led to tumours in both Sprague-Dawley and Wistar rats; at a dose level of 10 mg/week for 26 weeks, tumours have been induced at the site of injection of 33 of 41 rats." Adenine-1-*N*-oxide was inactive as a sulfate acceptor (*40*), a process that has been proposed as the second activating step for hydroxylamines and hydroxamic acids (*26,27*), although *in vivo* acetylation to 1-acetoxyadenine produced a reactive species toward *Bacillus subtilis*-transforming DNA and can be considered as a weak mutagen (*41*). The role of purine *N*-oxides in cancer has been reviewed (*43*).

The limited results we have obtained in the Ames mutagenicity test are not inconsistent with the metabolic-*N*-oxygenation hypothesis of toxication/detoxication of aminoazaheterocycles, which is a good guide to genotoxicity. Clearly, more bases and their corresponding *N*-oxides and hydroxylamines need to be prepared and tested at various concentrations using additional sophisticated bacterial test strains lacking specific xenobiotic-metabolizing enzyme systems before the concept can be fully substantiated.

REFERENCES

1. Gorrod, J. W., and Lam, S. P. Amino azaheterocycles: friend or foe? In: Molecular Aspects of Human Disease, Vol. 2 (J. W. Gorrod, O. Albano, and S. Papa, Eds.), Ellis Horwood, Chichester, UK, 1989, pp. 100–112.
2. Gorrod, J. W., and Lam, S. P. Microsomal cytochrome P-450 mediated N-oxygenation of aminoazaheterocycles. In: Biological Oxidation Systems, Vol. 1 (C. C. Reddy, G. A. Hamilton, and K. M. Madyastha, Eds.), Academic Press, San Diego, CA, 1990, pp. 147–162.
3. Gorrod, J. W., and Lam, S. P. The role of cytochrome P-450 in the biological nuclear N-oxidation of aminoazaheterocyclic drugs and related compounds. In: N-Oxidation of Drugs: Biochemistry, Pharmacology, Toxicology (P. Hlavica and L. A. Damani, Eds.), Chapman and Hall, London, 1991, pp. 157–184.
4. Sugimura, T., and Sato, S. Mutagens-carcinogens in foods. Cancer Res. 43: 2415s–2421s (1983).
5. Sugimura, T., Kawachi, T., Nagao, M., Yahagi, T., Seino, Y., Okamoto, T., Shudo, K., Kosuge, T., Tsuji, K., Wakabayashi, K., Itaka, Y., and Itai, A. Mutagenic principle(s) in tryptophan and phenylalanine pyrolysis products. Proc. Jpn. Acad. 53: 58–61 (1977).
6. Wolf, F. J., Steffens, J. J., Alvaro, R. F. and Jacob, T. A. Microsomal conversion of MK-302, arprinocid [6-amino-9-(2-chloro-6-fluorobenzyl) purine] to 6-amino-9-(2-chloro-6-flurobenzylpurine-1-N-oxide by liver microsomes from the chicken and the dog and to the 2-chloro-6-flurobenzyl alcohol by liver microsomes from rat and mouse. Fed. Proc. 37: 814 (1978).
7. Hubbel, J. P., Henning, M. L., Grace, M. E., Nichol, C. A., and Sigel, C. W. N-Oxide metabolites of the 2,4-diaminopyrimidine inhibitors of dihydrofolate reductase, trimethoprim, pyrimethamine and metoprine. In: Biological Oxidation of Nitrogen (J. W. Gorrod, Ed.), Elsevier, Amsterdam, 1978, pp. 177–182.
8. Hubbel, J. P., Kao, C. J., Sigel, C. W., and Nichol, C. A. Sex dependent disposition of metroprine by mice. In: Current Chemotherapy and Infectious Disease (J. D. Nelson and C. Grassi, Eds.), American Society for Microbiology, Washington, DC, 1980, pp. 1620–1621.
9. El-Ghomari, K., and Gorrod, J. W. Metabolic N-oxygenation of 2,4-diamino-6-substituted pyrimidines. Eur. J. Drug Metab. Pharmacokinet. 12: 253–258 (1987).
10. Watkins, P. J., and Gorrod, J. W. Studies on the in vitro biological N-oxidation of trimethoprim. Eur. J. Drug Metab. Pharmacokinet. 12: 245–258 (1987).
11. Lam, S. P., Devinsky, F., and Gorrod, J. W. Biological N-oxidation of adenine and 9-alkyl derivatives. Eur. J. Drug Metab. Pharmacokinet. 12: 239–243 (1987).
12. Lam, S. P., Barlow, D. J., and Gorrod, J. W. Conformational analysis of 9-substituted adenines in relation to their microsomal 1-N-oxidation. J. Pharm. Pharmacol. 41: 373–378 (1989).
13. Sugimura, T., and Nagao, M., Mutagenic factors in cooked foods. CRC Crit. Rev. Toxicol. 8: 189–209 (1979).
14. Ishida, Y., Negishi, C., Umemoto, A., Fujita, Y., Sato. S., Sugimura, T., Thorgeirsson, S. S., and Adamson, R. H. Activation of mutagenic and carcinogenic heterocyclic amines by S-9 from the liver of a rhesus monkey. Toxicol. in Vitro 1: 45–48 (1987).
15. Kato, R. Metabolic activation of mutagenic heterocyclic aromatic amines from protein pyrolysates. CRC Crit. Rev. Toxicol. 16: 307–347 (1986).
16. Kato, R., Kamataki, T., and Yamazoe, Y. N-Hydroxylation of carcinogenic and mutagenic aromatic amines. Environ. Health Perspect. 49: 21–25 (1983).
17. Gorrod, J. W., and Iles, N. C. The probable role of N-oxidation in a mechanism for the co-mutagenicity of norharman. Progress Pharmacol. Clin. Pharmacol. 8: 327–333 (1991).
18. Iles, N. Biological N-oxidation of isomeric aminopyridines PhD Thesis, University of London, 1988.
19. Stevens, M. A., and Brown, G. B. The structure of adenine-N-oxide. J. Am. Chem. Soc. 80: 2759–2762 (1958).
20. Giner-Sorolla, A., and Bendich, A. Synthesis and properties of some 6-substituted purines. J. Am. Chem. Soc. 80: 3932–3937 (1958).
21. Montgomery, J. A., and Temple, C. Synthesis of potential anticancer agents. XXVI. The alkylation of 6-chloropurine. J. Am. Chem. Soc. 83: 630–635 (1961).
22. Maron, D. M., and Ames, B. N. Revised methods for the Salmonella mutagenicity test. Mutat. Res. 113: 173–215 (1983).
23. Lam, S. P. Influence of 9-substitution on the microsomal N-oxidation of adenine. PhD Thesis, University of London, 1989.
24. Lam, S. P., and Gorrod, J. W. Screening for microsomal 1-N-oxidation of 9-substituted adenines. Prog. Pharmacol. Clin. Pharmacol. 8: 193–201 (1991).
25. Clement, B., and Kunze, T. Hepatic microsomal *N*-hydroxylation of adenine to 6-hydroxylaminopurine. Biochem. Pharmacol. 39: 925–933 (1990).
26. Miller, J. A., and Miller, E. C. The metabolic activation of carcinogenic aromatic amines and amides. Prog. Exp. Tumour Res. 11: 273–301 (1969).
27. Weisburger, J. H., and Weisburger, E. K. Biochemical formation and pharmacological, toxicological and pathological properties of hydroxylamines and hydroxamic acids. Pharmacol. Rev. 25: 1–66 (1973).
28. Kriek, E., Westra, J. G., and Welling, M. Reaction of N-oxidation products of aromatic amines with nucleic acids. In: Biological Oxidation of Nitrogen in Organic Molecules (J. W. Gorrod and L. A. Damani, Eds.), Ellis Horwood, Chichester, UK, 1985, pp. 366–376.
29. Saito, K., Yamazoe, Y., Kamataki, T., and Kato, R. Mechanism of activation of proximate mutagens in Ames tester strains: the acetyl-CoA dependent enzyme in Salmonella typhimurium TA98 deficient in

TA98/1,8-DNP$_6$ catalyzes DNA-binding as the cause of mutagenicity. Biochem. Biophys. Res. Commun. 116: 141–147 (1983).
30. Giner-Sorolla, A., and Benedich, A. Synthesis and properties of some 6-substituted purines. J. Am. Chem. Soc. 80: 3932 (1958).
31. Sartorelli, A. C., Beiber, A. L., Chang, P. K., and Fischer, G. A. Some inhibitory properties of 6-N-hydroxylamino purine: an analogue of adenine and hypoxanthine. Biochem. Pharmacol. 13: 507–515 (1964).
32. Freese, E. B. The mutagenic effect of hydroxyaminopurine derivatives on phage T4. Mutat. Res. 5: 299–301 (1968).
33. Barrett, J. C. Induction of gene mutation in and cell transformation of mammalian cells by modified purines: 2-aminopurine and 6-N-hydroxylaminopurine. Proc. Natl. Acad. Sci. USA 78: 5685-5689 (1981).
34. Knaap, A. G. A. C., and Simons, J. W. I. M. Induction of reverse mutations at the HGPRT locus in L5178Y mouse lymphoma cells. Mutat. Res. 85: 290 (1981).
35. McCartney, M., McCoy, E. C., Rosenkranz, H. S., and Giner-Sorolla, A. Carcinogenic N-hydroxylaminopurine derivatives do not act as base analog mutagens in *Salmonella typhimurium*. Mutat. Res. 144: 231–237 (1985).
36. Adbul-Masih, M. T., and Bessman, M. J. Biochemical studies on the mutagen, 6-N-hydroxylaminopurine. J. Biol. Chem. 261: 2020–2026 (1986).
37. Murray, V. Transversion-specific purine analogue mutagens and the mechanism of hydroxylaminopurine mutagenesis. Mutat. Res. 177: 189–199 (1987).
38. Sugiura, K., Teller, M. N., Parham, J. C., and Brown, G. B. A comparison of the oncogenicities of 3-hydroxyxanthine, guanine 3-N-oxides and some related compounds. Cancer Res. 30: 184–188 (1970).
39. Brown, G. B., Sugiura K., and Cresswell, R. M. Purine N-oxides XVI. Oncogenic derivatives of xanthine and guanine. Cancer Res. 25: 986-991 (1965).
40. McDonald, J. J., Strohrer, G., and Brown, G. B. Oncogenic purine N-oxide derivatives as substrates for sulfotransferase. Cancer Res. 33: 3319–3323 (1973).
41. McCuen, R. W., Strohrer, G., and Sirontak, F. M. Mutagenicity of derivatives of the oncogenic purine N-oxides. Cancer Res. 34: 378–384 (1974).
42. Brown, G. B. Purine N-oxides and cancer. Prog. Nucl. Acids Res. Mol. Biol. 8: 209–255, (1968).
43. Chaube, S., and Murphy, M. L. Teratogenic effects of 6-hydroxylaminopurine in the rat-protection by inosine. Biochem. Pharmacol. 18: 1147–1156 (1969).